



Buprenorphine Treatment for Opioid Use Disorder: An Overview

Matisyahu Shulman^{1,2} · Jonathan M. Wai^{1,2} · Edward V. Nunes^{1,2}

Published online: 6 May 2019
© Springer Nature Switzerland AG 2019

Abstract

Opioid use disorder affects over 26 million individuals worldwide. There are currently three World Health Organization-recommended and US Food and Drug Administration-approved medication treatments for opioid use disorder: the full opioid agonist methadone, the opioid partial agonist buprenorphine, and the opioid receptor antagonist naltrexone. We provide a review of the use of buprenorphine for the treatment of opioid use disorder and discuss the barriers, challenges, risks, and efficacy of buprenorphine treatment vs. other treatments. Although evidence from numerous studies has shown buprenorphine to be effective for the treatment of opioid use disorder, a majority of patients with opioid use disorder do not receive buprenorphine, or any other medical treatment. We review the different formulations of buprenorphine, including newer long-acting injectable formulations that may decrease the risk of diversion and improve adherence.

Key Points

Buprenorphine is an effective maintenance treatment for opioid use disorder.

Use of buprenorphine as a medically supervised withdrawal medication without maintenance pharmacotherapy to promote abstinence leads to high rates of relapse (over 90% in some studies).

Risks of buprenorphine when used for maintenance treatment most commonly include sedation, diversion, and constipation.

New long-acting formulations of buprenorphine may help adherence while decreasing abuse and diversion liability.

1 Opioid Use Disorder

Opioid use disorder affects over 26 million individuals worldwide, with the highest prevalence in the high-income countries of North America [1]. It is estimated that 2.4 million Americans currently have opioid use disorder, including individuals in virtually every region of the USA. [2]. The prognosis for opioid use disorder is poor if left untreated, with significant morbidity and mortality resulting from opioid overdose [3]. Three medication treatments are recommended by the World Health Organization [4] and are US Food and Drug Administration (FDA) approved for the treatment of opioid use disorder: (1) the opioid receptor full agonist methadone, (2) the opioid receptor antagonist naltrexone (first approved in an oral form for daily administration, and more recently as an extended-release monthly injection; brand name: Vivitrol[®]), and (3) the opioid receptor partial agonist buprenorphine, available as sublingual or buccal tablets or films, a skin patch (indicated for pain management), and extended-release parenteral formulations (injection or implant) [5]. When taken as directed, these medications are highly effective, enabling a large proportion of patients to achieve either abstinence or a substantial reduction in opioid use, also reducing the risk of overdose if a patient uses opioids. However, most people with opioid use disorder are not receiving medication treatment, a gap that urgently needs to be filled [6, 7]. Of these available medications, buprenorphine is currently the most widely prescribed and has, arguably, the greatest potential for

✉ Matisyahu Shulman
matisyahu.shulman@nyspi.columbia.edu

¹ New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032, USA

² Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, USA

widespread dissemination owing to its relative ease of use and safety. In what follows, we review the history, mechanism, evidence for effectiveness, and available formulations of buprenorphine.

2 Prototype of the Agonist Treatment Strategy

Methadone was the first medication treatment for opioid use disorder, and the prototype of the agonist treatment strategy of which buprenorphine is another example. Methadone was first synthesized in Germany in the 1940s as a synthetic opioid analgesic and is still used for the management of severe pain [8]. Methadone is potent, orally bioavailable with slow absorption (by the oral route), and has a long half-life (approximately 24 h). Hallmarks of the agonist treatment strategy for addiction treatment include slow absorption, which reduces the tendency to produce a rush or “high,” and slow elimination, which avoids the rapid emergence of withdrawal symptoms [9].

Methadone maintenance treatment for opioid use disorder was first developed and shown to be effective by Dole, Nyswander, and Kreek in the 1960s [10, 11]. They hypothesized that heroin addiction was a disease of the brain with behavioral manifestations and not simply a personality disorder or criminal behavior. Methadone was studied to find a medication to: (1) prevent opiate withdrawal; (2) reduce “drug hunger” or craving; and (3) normalize physiologic functions. Methadone also had the added benefit of a “narcotic blockade” to prevent euphoria from additional opiate use [12]. When titrated to the effective dose range (80–120 mg per day), methadone produces a blockade of opioid effects, presumably by inducing tolerance [10]. When patients use heroin or other illicit opioids while maintained on adequately dosed methadone, they often report something to the effect: “I felt nothing, realized I was wasting my money, so I stopped using.” Tolerance also presumably underlies the effect of methadone to protect against opioid overdose. Much of the early methadone literature was focused on the public health concerns of criminality and unemployment that occur concomitantly with heroin addiction. Methadone was shown to decrease criminal behavior [13], human immunodeficiency virus, and other infectious disease risk, while also promoting abstinence, and protecting against overdose [14, 15].

Buprenorphine for opioid use disorder works as a maintenance treatment with a long duration of action [16], with the added benefit of providing only partial mu-opioid receptor agonism along with high receptor affinity [17]. These neurophysiological properties make buprenorphine attractive as a long-term maintenance treatment of opioid use disorder. The high receptor affinity of buprenorphine protects against both

overdose and reinforcing effects in the case of use with full agonist opioids. At the same time, the only partial agonism at the mu-opioid receptor prevents overdose and intoxication related to buprenorphine itself.

3 Barriers to Dissemination of Medication Treatments for Opioid Use Disorder

Despite the numerous studies that have documented the safety and efficacy of methadone, buprenorphine, and extended-release injectable naltrexone (XR-naltrexone) in treating opioid use disorder [18], access to these treatments remains limited. This is in part owing to safety concerns—initiation of methadone can increase the risk of overdose if the dose is raised too quickly or combined with illicit drugs before tolerance has fully set in. Prescription of methadone for the treatment of opioid use disorder is usually government regulated, with the stringency of regulations differing by country. In the USA, methadone is limited by federal law to specially licensed, closely regulated clinics that must operate under strict guidelines—requiring, for example, that patients attend the clinic daily at the outset for observed dosing. These barriers associated with methadone treatment limit its attractiveness and acceptability to patients. Individuals without convenient access to specialized methadone clinics are significantly less likely to enroll in treatment [19]. In contrast France, the UK, and Canada all allow methadone to be prescribed by a physician with no special training and to be dispensed by a community pharmacy with less restrictive regulation [20, 21].

Buprenorphine, in contrast, has less restrictive restrictions in many countries. It was introduced to the USA for the treatment of opioid use disorder under the Drug Addiction Treatment Act of 2000 [22], which allows it to be prescribed on an outpatient basis by any licensed physician (or nurse practitioner or physician assistant) who has undergone a modest amount of training and received a “waiver” certifying completion of training. In the USA, buprenorphine can be dispensed at any retail pharmacy.

With regard to the clinical barriers associated with starting a medication for opioid use disorder, buprenorphine is relatively easy to initiate. In contrast to XR-naltrexone, which requires patients to be fully withdrawn before the medicine can be initiated, buprenorphine only requires patients to manifest at least mild withdrawal symptoms, at which point the medication can be started. Because of its relative ease of use, buprenorphine has great potential for widespread dissemination across the treatment system. Despite this, there is still a shortage of buprenorphine providers. Even in developed countries such as the USA, many providers either do not or minimally prescribe buprenorphine

[23–25]. In many developing countries, buprenorphine may not be available at all [26, 27].

4 Development, Indications, and Regulatory Status

In 1966, John Lewis, at Reckitt and Coleman, which was then primarily a home products company, discovered buprenorphine [28]. The goal had been to develop an opioid analgesic with less abuse potential. After its discovery, trials began through the Addiction Research Center at the Federal Narcotics Hospital in Lexington, Kentucky. In 1975, at the Committee on Problems of Drug Dependence, Donald Jasinski proposed buprenorphine as an attractive alternative to methadone for opioid treatment because of its unique profile as a mu-opioid receptor partial agonist, producing less tolerance and less intoxicating effects. This includes less respiratory depression compared with full agonists, as well as a blockade of opioid effects at adequate doses (similar to the antagonist naltrexone) owing to its high receptor affinity [29]. A long serum half-life (approximately 28–37 h if taken sublingually) [16] and a long duration of activity at receptors contribute to the attractiveness of its mechanism as a treatment for opioid use disorder. Buprenorphine was also found to be a kappa-opioid receptor antagonist. Agonists at the kappa receptor produce dysphoric effects, and thus it has been hypothesized that antagonists at the endogenous kappa system might oppose the dysphoria that accompanies withdrawal from opioids, or exert antidepressant effects [30, 31].

4.1 Buprenorphine as an Analgesic

Buprenorphine was first approved for clinical use as an analgesic in a parenteral formulation for acute and post-operative pain. In the UK, buprenorphine was approved in 1978 and marketed for pain in an injectable form, and several years later in a sublingual form. In the USA, parenteral buprenorphine (brand name: Buprenex[®]) was approved for acute or post-operative pain in 1985. Buprenorphine was subsequently formulated as a skin patch (brand name: Butrans[®] patch) with a 1-week duration of effect for the treatment of subacute or chronic pain. Recently, a buccal film (brand name: Belbuca[®]) has also been approved in the USA for the treatment of pain. This indication is particularly relevant for individuals with comorbid pain and opioid use disorder as buprenorphine may be helpful as a treatment for both. The patch or buccal film are good alternatives for patients requiring opioid analgesia who also manifest signs of opioid misuse (taking more than the prescribed dose, requesting increased doses in the absence of changes in the underlying cause of the pain), or develop opioid use disorder.

4.2 Buprenorphine for the Treatment of Opioid Use Disorder: Regulatory Status and Training Requirements

Buprenorphine, by the sublingual route of administration, was initially adopted as an office-based outpatient treatment for opioid use disorder in France in the 1990s, and was later FDA approved in the USA in 2002. Buprenorphine is currently approved for the indication of opioid use disorder maintenance treatment in more than 45 countries. It has been included in the World Health Organization model list of essential drugs [32], and recent efforts have expanded the use of buprenorphine in many countries that had previously not had access [33–35]. However, many barriers still exist [36].

For the opioid substitution medications, most countries have strict restrictions on who may prescribe or administer these medications, and in what setting. Swedish opioid agonist treatment programs have strict inclusion and exclusion criteria, excluding illicit use of specific opioids [37]. In India, opioid use disorder agonist maintenance treatment is delivered only by government-run centers and acquired immune deficiency syndrome-based non-government organizations [38]. In some countries, such as Russia, opioid agonist maintenance treatment is not offered at all [39].

France, in contrast, adopted outpatient maintenance with buprenorphine for general practitioners in response to a growing opioid problem in the country. A feasibility study performed in France, starting in 1993, found that outpatient treatment of 50 individuals with buprenorphine maintenance was both feasible and clinically effective with opioid-positive urine toxicology decreasing from close to 100% at baseline to below 10% after 12 months of treatment [40]. Based on this experience, the French policy surrounding the use of buprenorphine facilitated its use in the community starting in 1996. No additional training requirements were imposed on prescribers; there were no specific urine testing requirements, and pharmacists were allowed to observe the patient taking the medication, if specified by the physician. By 2001, about 75,000 individuals were prescribed buprenorphine in France, mostly by primary care physicians [41]. Nationwide rates of opioid overdose in France were dramatically reduced after the introduction of buprenorphine, supporting the clinical effectiveness of buprenorphine and the public health initiative under which it was introduced [42].

In the USA, regulatory restrictions on the use of opioid agonists (or partial agonists) for the treatment of opioid use disorder required new legislation to allow for the use of buprenorphine outside of supervised administration clinics. An initial proposal was made in 1995 to amend the law to allow for outpatient prescription, and this was eventually approved after a lengthy debate and revision process in 2000—the Drug Addiction Treatment Act of 2000. In 2002,

the FDA approved buprenorphine for the use of opioid use disorder [22].

Under the US Drug Addiction Treatment Act of 2000, buprenorphine can be dispensed by a non-specialized pharmacy if prescribed by any medical practitioner who has undergone an 8-h training course on the use of buprenorphine. Recently, in response to the growing opioid epidemic in the USA, the Federal Government, through the Substance Abuse and Mental Health Services Administration, funded the Prescribers Clinical Support System for Medication Assisted Treatment [43]—a free web-based training resource offering the required 8-h training course through the Providers Clinical Support System at <https://pcssnow.org>. In addition, there are web-based training modules on a range of related topics relevant to the treatment of opioid use disorder (such as psychiatric and medical co-occurring disorders), and the evaluation and management of pain.

The law also placed a limit of 30 individuals treated by a given provider at any one time. A later addendum allowed for providers to request to increase this number to 100 individuals after a minimum of 1 year at the capacity of 30. More recently, the upper limit on the number of patients prescribed per prescriber was increased to 275 for individuals who have had a waiver to treat 100 patients for at least a year and who meet certain requirements. This includes having specialized certification as an addiction specialist or working in treatment programs meeting specific requirements. The law was also modified to allow physician assistants and nurse practitioners to prescribe as well, after completion of an expanded 24-h training course.

5 Effectiveness of Buprenorphine for Medically Supervised Opioid Withdrawal

When individuals have taken opioids regularly over a sustained period of time (either illicitly or for pain management), physiologic dependence develops, and abrupt cessation of opioids produces a characteristic withdrawal syndrome. Signs and symptoms may include autonomic hyperactivity (sweating, chills, lacrimation, tremor, pupillary dilatation, and piloerection), gastrointestinal distress (nausea, intestinal cramping, diarrhea, vomiting), yawning, rhinorrhea, sneezing, body aches, anxiety, and dysphoria. Though rarely life threatening, opioid withdrawal is extremely unpleasant, and is the main driver of continued opioid use among those who have developed physiological dependence and/or opioid use disorder. Opioid withdrawal can be treated with a slow taper of opioid dosage, preferably with an agent with a long half-life such as methadone or buprenorphine, to avoid abrupt variations in systemic exposure to opioids. Opioid withdrawal can also be treated

with non-opioid medications such as adrenergic alpha-2 receptor antagonists (e.g., clonidine, lofexidine, guanfacine, tizanidine), which reduce autonomic symptoms, and other symptomatic treatments, e.g., benzodiazepines for anxiety, non-opioid analgesics for pain, or anti-emetics for gastrointestinal distress [44].

Given its long half-life, high receptor affinity, and slow dissociation from receptors, buprenorphine is an attractive candidate for medically supervised opioid withdrawal. Patients must manifest at least mild withdrawal to comfortably initiate buprenorphine (see also below), and when initiated at that point, buprenorphine relieves withdrawal symptoms. A typical regimen would escalate the dose to relieve withdrawal over the first 1–2 days, typically to 8–12 mg per day, and then taper the dose by 2–4 mg per day until discontinued. Large clinical trials have shown that buprenorphine, dosed in this manner, is more effective than a non-opioid, clonidine-based medically supervised withdrawal for outcomes of both withdrawal discomfort and successful completion of medically supervised withdrawal [45, 46].

5.1 Risk of Relapse and Opioid Overdose for Medically Supervised Withdrawal from Opioids

After completion of medically supervised withdrawal (whether it be via a methadone taper, buprenorphine taper, or non-opioid medications), the rate of relapse to opioid use is very high [47]. For example, in a trial among patients with opioid use disorder dependent on prescription opioids, over 90% of patients had returned to opioids within the next 2 months after a 12-week period of stabilization and taper off buprenorphine [48]. Thus, medically supervised withdrawal by itself is not favored for the treatment of opioid use disorder, even if followed by intensive inpatient treatment or ongoing counseling. In fact, the risk of opioid overdose has been shown to be elevated in the immediate period after release from inpatient treatment programs or jails where medically supervised withdrawal would have taken place [49–52]. Medically supervised withdrawal reduces physiological tolerance, meaning that individuals will be more sensitive to the effects of opioids, including respiratory depression that leads to overdose and death.

5.2 Buprenorphine in the Initiation of Naltrexone

Initiation of naltrexone requires that a patient with opioid use disorder and current physiological dependence first be fully withdrawn so that little or no opioid agonist remains on receptors. This is because naltrexone, as an antagonist with high receptor affinity, will displace opioid agonists still present on receptors, producing an abrupt drop in agonist effect that results in precipitated opioid withdrawal. Precipitated

withdrawal can be quite severe, and risks driving a patient from treatment and back to illicit opioids. Buprenorphine was suggested as a good, medically supervised withdrawal strategy for a lead-in to naltrexone, on the theory that as a partial agonist, it can serve as a stepping stone between full agonists, such as heroin, and antagonists like naltrexone [53]. Subsequently, various strategies for medically supervised withdrawal and transition to naltrexone have been demonstrated, often involving a combination of a brief buprenorphine taper with clonidine and other non-opioid medications helpful in the treatment of withdrawal [44].

Buprenorphine and naltrexone have relatively similar affinities for the mu-opioid receptor, such that a substantial dose of naltrexone given to an opioid-dependent individual who still has buprenorphine on the receptors would displace buprenorphine. This would then produce a net reduction in opioid agonist effect, and precipitated withdrawal symptoms. Clinical experience bears this out and administration of a full dose of oral naltrexone (50 mg) soon after the last dose of a buprenorphine taper may precipitate withdrawal. However, a buprenorphine-naltrexone cross-taper strategy for initiation of XR-naltrexone has been shown to be feasible, involving a brief (2–3 days) exposure to low-dose buprenorphine (8–10 mg total) and escalating doses of oral naltrexone beginning with very low doses (1–3 mg per day) [54].

6 Effectiveness of Buprenorphine for Long-Term Treatment of Opioid Use Disorder

The main indication for buprenorphine is the long-term treatment of opioid use disorder, namely opioid maintenance treatment. Since it was originally suggested as a potentially useful maintenance agent, numerous controlled clinical trials have tested the effectiveness of buprenorphine compared to placebo, buprenorphine compared to methadone, and lower compared to higher doses of buprenorphine. A recent Cochrane meta-analysis [18], based on a search of the literature up to January 2013, identified 31 randomized clinical trials (5340 patients in total across trials) comparing sublingual buprenorphine to either placebo or methadone for maintenance treatment of opioid use disorder. Trials were classified according to the buprenorphine dose conditions studied as either fixed-dose studies (for buprenorphine, low dose: 2–6 mg per day; medium dose: 7–15 mg per day; or high dose: ≥ 16 mg per day; and for methadone, low dose: ≤ 40 mg/day; medium dose: 45–85 mg/day; or high dose: > 85 mg/day), or flexible-dose studies, with medication doses advanced as needed. Trial lengths ranged between a few weeks to 1 year, and retention in treatment was the main outcome reported by most trials. Retention in treatment is, arguably, the most important outcome because

most patients who continue to take an opioid maintenance treatment (buprenorphine, methadone, or naltrexone) will either cease opioid use, or use much less. Various measures of opioid use, other drug use, and functioning were also reported by some trials.

6.1 Buprenorphine vs. Placebo

In the Cochrane meta-analysis [18], buprenorphine, across low (2–6 mg per day), medium (7–15 mg/day), and high (≥ 16 mg/day) doses was superior to placebo in improving retention in treatment, but only high-dose buprenorphine (≥ 16 mg per day) reduced opioid use significantly compared with placebo [18]. This suggests the importance of a higher dosage to achieve the best effects from buprenorphine.

6.2 Buprenorphine vs. Methadone

In the Cochrane meta-analysis [18], fixed-dose studies found no significant difference on retention in treatment between medium-dose buprenorphine and medium-dose methadone, or between high-dose buprenorphine and high-dose methadone. In contrast, flexible dosing, which describes doses increased as needed to achieve abstinence, is arguably most relevant to the clinical practice of methadone; this process yielded significantly better retention in treatment, although opioid use outcomes were similar. It should be noted that the raw rates of retention in treatment combined across these studies for descriptive purposes show high rates of dropout across conditions. For example, across the 11 flexible dosing studies (the trials having best overall retention in treatment rates), retention to study completion was 53% (367/697) on buprenorphine and 63% (437/694) on methadone.

Similar findings issued from a recent large-scale multi-site trial conducted in the National Institute on Drug Abuse-funded Clinical Trials Network, which randomized 1267 patients seeking treatment for opioid use disorder at traditional opioid treatment programs (i.e., methadone maintenance programs) to maintenance treatment with either methadone (mean dose 93 mg, range 5–397 mg) or buprenorphine (mean dose 22 mg, range 2–32 mg), flexibly dosed to effect. The proportion of patients retained in treatment at 6 months was significantly lower on buprenorphine (46%) compared with methadone (74%), while urine-confirmed opioid abstinence was similar between the two groups [55]. Importantly, both retention in treatment and abstinence were associated with higher dosages for both methadone and buprenorphine. Among patients treated with buprenorphine at the high end of the dose range (30–32 mg/day), retention at 6 months was 60% although 30% of those still had opioid-positive urine tests, suggesting that even higher doses might be explored in future studies. Over a 4-year follow-up of the cohort of patients from this study, not being on medication (either

buprenorphine or methadone) was strongly associated with relapse to opioid use [56].

6.3 Buprenorphine vs. Extended-Release Injectable Naltrexone

XR-naltrexone (brand name: Vivitrol®) is indicated for the maintenance treatment of opioid use disorder with a 380-mg intramuscular injection once every 4 weeks. XR-naltrexone was FDA approved for the treatment of opioid use disorder on the basis of a double-blind placebo-controlled trial conducted in Russia that showed XR-naltrexone was superior to placebo on opioid-negative urine tests and on retention in treatment [57]. The proportion of patients retained at the end of the 6-month trial on XR-naltrexone was 53.2%, suggesting a substantial rate of dropout. However, dropout rates were in a similar range to that observed in other trials with sublingual buprenorphine [58].

Sublingual buprenorphine was subsequently directly compared with XR-naltrexone in a 6-month open-label trial conducted in the National Institute on Drug Abuse Clinical Trials Network, comparing sublingual buprenorphine ($N=287$), flexibly dosed to effect (median maintenance dose: 16 mg/day) with monthly injections of XR-naltrexone ($N=283$) [59]. Participants were recruited and randomized as inpatients, and started on their assigned medication as soon as possible thereafter. The primary outcome measure was a binary indicator, termed “relapse,” defined as either return to regular opioid use according to self-report or urine toxicology, or dropout from treatment. Among all randomized patients, buprenorphine was modestly superior to XR-naltrexone on the primary outcome of relapse, and on the number of opioid-positive urine tests. The rate of relapse by the end of 24 weeks was 57% on buprenorphine vs. 65% on a naltrexone injection. Most of this difference could be accounted for by the induction hurdle, wherein 27% of patients assigned to XR-naltrexone did not initiate medication (most of these subsequently meeting relapse criteria) while nearly all individuals assigned to buprenorphine successfully started on the medication. In a per-protocol secondary analysis only considering outcomes for individuals who were inducted onto the assigned medication, relapse rates were not significantly different between the two medications. Again, it is notable that over 50% of patients treated with buprenorphine in this study failed to be retained in treatment for 6 months without relapse.

6.4 Summary

Buprenorphine, compared with placebo, improves retention in treatment at low, medium, and high doses. Compared with methadone, buprenorphine has lower retention rates but similar rates of abstinence among those retained. Higher doses

of buprenorphine increase retention and abstinence rates. Buprenorphine is modestly superior to XR-naltrexone in preventing relapse or dropout from treatment and in increasing abstinence rates—a difference that may be accounted for mainly by the ease of initiating buprenorphine, compared to the induction hurdle of initiating naltrexone. Across trials, retention in treatment for buprenorphine is in the range of 50% or less at 6 months, highlighting the need for strategies to improve long-term adherence to buprenorphine.

7 Clinical Management Issues

7.1 Importance of Adequate Dosage

A common theme emerging from the above reviewed studies of buprenorphine for the long-term maintenance treatment of opioid use disorder is that higher doses are associated with better retention in treatment and a higher likelihood of abstinence. Once buprenorphine is initiated, the dose can be advanced rapidly because its partial agonism limits typical opioid side effects, including the risk of over-sedation or overdose. Future research should focus more attention on dose titration strategies and possibly on exploring doses beyond the 24- to 32-mg range, which has been the maximum in most studies to date.

7.2 Initiation of Buprenorphine

Initiation of buprenorphine among patients actively using opioids, which would include most individuals presenting as outpatients, requires a delay of the first dose until the patient begins to manifest at least mild-to-moderate opioid withdrawal. This is to avoid precipitated withdrawal, which may occur if there is still substantial receptor occupancy by full mu-opioid agonists at the time buprenorphine is first given. Buprenorphine has a greater affinity and binds more strongly to opioid receptors than heroin, morphine, or other common opioid analgesics, making it a strongly binding partial agonist that displaces full agonists from the receptors. This produces an abrupt net drop in opioid agonist effect, leading to symptoms of precipitated opioid withdrawal. Precipitated withdrawal can be more severe than spontaneous withdrawal (withdrawal that emerges gradually after discontinuation of agonists), and delirium has been rarely observed [60]. The recommended procedure for buprenorphine initiation is to wait for the development of mild-to-moderate withdrawal symptoms, and to then administer a test dose of 2–4 mg of sublingual buprenorphine. Typically, the test dose will result in some relief of withdrawal, which indicates it is safe to increase the dose. Buprenorphine is typically increased in 2- to 4-mg increments, up to 12 mg total on the first day and then titrated up over the next 2 days up to 24 mg. When

it was first approved in the USA, treatment guidelines suggested that buprenorphine initiation take place under direct clinical supervision to confirm sufficient withdrawal symptoms, and to directly observe the response to the test dose. However, it subsequently has become clear that most patients can safely initiate buprenorphine at home, following instructions to wait for moderate withdrawal to develop, with phone back-up in case of questions or problems [61].

7.3 Fentanyl and Buprenorphine Initiation

Fentanyl is an ultra-high potency full opioid agonist (50–100 times the potency of morphine), which has now infiltrated the illicit heroin supply in many parts of the USA. Recently, it has been noted that large proportions of urine samples of patients presenting for treatment are testing positive for fentanyl in many locations [62]. Anecdotal reports suggest that the presence of fentanyl in a patient's system is complicating buprenorphine initiation with reports of precipitated withdrawal occurring beyond the timeframe where it would normally be expected. This may be owing to the high lipophilicity of fentanyl, with fentanyl remaining present in the brain and on receptors even after urine toxicology no longer detects it, and/or the high intrinsic activity of fentanyl at the receptors, such that displacement of fentanyl from even a small number of receptors produces a substantial drop in opioid signaling. Thus, greater caution may be warranted when initiating buprenorphine in the presence of fentanyl.

7.4 Retention in Treatment and the Problem of Poor Adherence

The above review of the effectiveness trials of sublingual buprenorphine has highlighted the problem of substantial rates of dropout from treatment. Dropout carries a high risk of relapse to opioid use, and relapse carries a risk of overdose and death—a risk that has been particularly compounded by the emergence of illicit fentanyl in heroin supplies. Multiple reasons likely underlie dropout, including variable motivation for treatment, ongoing withdrawal symptoms or craving, overconfidence (believing medication is no longer needed), or stigma attached to relying on a medication to treat opioid dependence. More research is needed on how to improve adherence to buprenorphine treatment. Aggressive dosing and dose escalation, as reviewed above, are likely to be helpful. Some behavioral treatments delivered with buprenorphine have also shown promise, including contingency management (e.g., rewarding patients for treatment attendance or opioid-negative urine tests [63] and involving partners/family members to support the treatment plan [64]).

7.5 Duration of Treatment and Risk of Relapse after Discontinuation

Among patients successfully maintained on buprenorphine, the question becomes at what point is it safe to discontinue the medication? Unfortunately, the data on the appropriate duration of treatment, while limited, suggest a high risk of relapse to opioid use when buprenorphine (or methadone) is discontinued. As noted earlier, a large study conducted in the National Institute on Drug Abuse Clinical Trials Network found high relapse rates with discontinuation of buprenorphine early in treatment [48]. Long-term follow-ups of this sample, as well as the sample from the comparative effectiveness trial of buprenorphine vs. methadone described previously [56], show that the strongest predictor of abstinence from opioids over the long term is being on a maintenance medication (buprenorphine or methadone).

8 Risks and Side Effects

As an opioid partial agonist, buprenorphine may produce typical opioid side effects such as constipation and sedation. The most serious risk in the treatment of patients with opioid use disorder is opioid overdose, which is inherent in the disorder. Risk of overdose has been increasing in the population with opioid use disorder, owing partly to the advent of the higher potency fentanyl in the illicit heroin supply. Like other opioids, buprenorphine may suppress respiration, but less so compared with full opioid agonists. Because of its high receptor affinity, at adequate doses, buprenorphine will block the effects of other opioids, protecting against overdose. Thus, as with other medication treatments for opioid use disorder (methadone, naltrexone), the greatest risk of overdose is the discontinuation of buprenorphine and subsequent loss of the protection afforded. However, overdoses have also been observed when buprenorphine is combined with alcohol or sedative drugs, such as benzodiazepines [65], and in cases of accidental overdose in young children [66]. Patients should be warned about the risks of overdose in general, and the potential overdose risk when alcohol or sedatives are combined with buprenorphine.

Other potentially serious adverse effects listed in buprenorphine prescribing information include serotonin syndrome and adrenal insufficiency, although these are rare. Allergic reactions and local skin reactions to skin patches, or injected or implanted formulations may occur, as well as anaphylaxis (rarely). Androgen deficiency can be a consequence of long-term opioid exposure. Hepatitis or elevated liver enzymes have been reported to be associated with buprenorphine treatment. However, a large, randomized, post-marketing liver safety study (START) yielded no evidence of liver toxicity as a result of buprenorphine

compared to methadone, which is not thought to be liver toxic [67]. Elevated liver enzymes in a patient treated with buprenorphine should prompt consideration of other causes of hepatitis common in this population, including alcoholic hepatitis or viral hepatitis.

9 Metabolism and Drug Interactions

The most serious drug interactions involve co-administration of buprenorphine with central nervous system depressant drugs (e.g., alcohol, benzodiazepines, also muscle relaxants), which may increase intoxication or lead to overdose. Buprenorphine is metabolized by the hepatic cytochrome P450 (CYP) 3A4 enzyme to norbuprenorphine with subsequent glucuronidation. Thus, when prescribing buprenorphine, it is important to be mindful of co-administered drugs that inhibit or induce CYP3A4 as these may increase or decrease (respectively) buprenorphine blood concentrations. Buprenorphine functions as an inhibitor of CYP2D6 and CYP3A4, and thus may increase the concentrations of drugs metabolized by either of those pathways. Prescribing information for buprenorphine products also suggests caution with respect to the co-administration of serotonergic drugs or monoamine oxidase inhibitors owing to the risk of serotonin syndrome. This, however, is rare with buprenorphine and buprenorphine is routinely prescribed with serotonergic medications in clinical practice.

10 Use in Pregnancy

Treatment of women with opioid use disorder who are also pregnant requires special consideration because of concern for the health of the fetus and mother and issues of neonatal abstinence syndrome after birth. Use of agonist medication for individuals who are pregnant with opioid use disorder has been studied in several trials. Historically, methadone has been the treatment of choice for pregnant individuals with opioid use disorder. Use of methadone maintenance avoids the requirement for the brief period of withdrawal before induction required with buprenorphine. Any opioid withdrawal is generally avoided because of associations with seizures and death in the fetus, although some have argued that women may safely undergo medically supervised withdrawal without increased neonatal risk [68]. Methadone does have a significant drawback owing to its long half-life and full receptor agonism, as infants born to mothers who are maintained on methadone often experience a prolonged syndrome of withdrawal after birth, requiring treatment in a neonatal intensive care unit. A large randomized trial called the MOTHER trial compared methadone and buprenorphine to determine the relative safety of each in terms of maternal

and neonatal outcomes. The trial found that buprenorphine was superior to methadone in terms of a briefer length of neonatal abstinence syndrome after birth, and that women were significantly more likely to stay in treatment if randomized to methadone [69]. A meta-analysis of several cohort and randomized trials has found no difference between the two treatments in terms of adverse effects on the neonate [70].

Clinically, buprenorphine without naloxone is considered a viable alternative to methadone as an option for pregnant women with opioid use disorder. There may be a greater risk of dropout during pregnancy compared with methadone, but less risk of neonatal abstinence syndrome for infants born to mothers maintained on buprenorphine. For the treatment of neonatal abstinence syndrome, a recent meta-analysis found that buprenorphine was associated with a shorter hospital stay and length of treatment when compared with other medications such as methadone and morphine [71].

11 Buprenorphine Formulations

The various formulations of buprenorphine for the treatment of pain and opioid use disorder are summarized in Table 1.

11.1 Sublingual Buprenorphine and Buprenorphine-Naloxone Tablets and Film

The original formulations of buprenorphine that the FDA approved for the treatment of opioid use disorder were sublingual tablets, containing either buprenorphine alone (original brand name: Subutex[®]), sometimes referred to as the “mono product,” and tablets combining buprenorphine and naloxone (original brand name: Suboxone[®]). Sublingual administration is necessary because buprenorphine is well absorbed through the oral mucosa, but poorly bioavailable if ingested. Patients need to be instructed on how to use the sublingual tablets (to hold under the tongue until fully dissolved, and not swallow or drink liquids in the time period surrounding dosing). The addition of the short-acting opioid antagonist naloxone to buprenorphine was developed on the theory that this would discourage misuse of the medication by intravenous injection—naloxone is not well absorbed by the sublingual route, but it would cause precipitated withdrawal if injected. The buprenorphine-naloxone combination product is recommended for maintenance treatment of opioid use disorder. Buprenorphine alone (the mono product) may be preferable for medically supervised withdrawal where exposure to naloxone might worsen withdrawal symptoms, and is also recommended for use during pregnancy to avoid exposure of the developing fetus to naloxone.

Several generic buprenorphine-naloxone tablets are now available. Reckitt (the manufacturer of Suboxone)

Table 1 Buprenorphine formulations

Buprenorphine formulation (brand name, generic name, year of FDA approval)	Dose range	Formulations	Time to peak concentration (h)	Mean half-life (h)	Comments
Indicated for pain					
Intravenous/intramuscular (Buprenex, buprenorphine hydrochloride, 1985)	0.3–0.6 mg q6 h/PRN	0.3 mg	<1	1.2–7.2	For acute or post-operative pain
Transdermal system (Butrans, buprenorphine transdermal system, 2010)	5 mcg/h (if <30 mg oral morphine equivalents per day) or 10–20 mcg/h (if 30–80 mg oral morphine equivalents per day)	5, 7.5, 10, 15, 20 mcg/h	72	26 (after patch removal)	7-day transdermal patch
Buccal film (Belbuca, buprenorphine buccal film, 2015)	75 mcg daily or q12 h (for first 4 days)—900 mcg q12 h	75, 150, 300, 450, 600, 750, 900 mcg	2.5–3	16.4–38.8	Dosed daily or q12 h, has an adhesive and blocking layer to help fully absorb, peppermint flavored
Indicated for opioid use disorder					
Sublingual tablet (Subutex [now only generic], buprenorphine, 2002)	2–8 mg daily (first day)—24 mg daily	2 mg, 8 mg	1.6–4.0	31–35	May be safer for use in pregnancy because does not contain naloxone
Sublingual film (Suboxone [also generic], buprenorphine and naloxone, 2002)	2–8/0.5–2 mg daily (first day)—24/6 mg daily	2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg (buprenorphine/naloxone)	0.5–2.5	24–42 (buprenorphine), 2–12 (naloxone)	Sublingual film absorbs faster than the tablet
Sublingual tablet (Zubsolv, buprenorphine and naloxone, 2013)	1.4–2.8/0.36–0.72 mg (1st dose, up to 5.7/1.4 mg 1st day)—17.1/4.2 mg daily	0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg (buprenorphine/naloxone)	0.5–2.5	24–42 (buprenorphine), 2–12 (naloxone)	Higher bioavailability vs. Subutex or Suboxone, 2.9 mg of buprenorphine in Zubsolv equivalent to 4 mg in Suboxone
Buccal film (Bunavail, buprenorphine and naloxone, 2014)	2.1/0.3–12.6 mg/2.1 mg daily	2.1 mg/0.3 mg, 4.2 mg/0.7 mg, 6.3 mg/1 mg (buprenorphine/naloxone)	0.5–2.5	16.4–27.5 (buprenorphine), 1.9–2.4 (naloxone)	Has an adhesive and blocking layer to help fully absorb, citrus flavored
Implant (Probuphine, buprenorphine implant, 2016)	74.2 mg (1 dose only), 4 implants at a time	74.2 mg of buprenorphine per implant released over 6 months	12	24–48	Cannot be dosed more than 8-mg sublingual equivalents daily; implants must be removed after completion of 6-month dosing interval
Long-acting injectable (Sublocade, buprenorphine extended release, 2017)	300 mg first 2 months, 100 mg monthly after	100 mg/0.5 mL, 300 mg/1.3 mL prefilled syringe	24	Terminal plasma half-life: 43–60 days	Subcutaneous injection in abdomen; forms a hard nodule in subcutaneous space, requires refrigeration before administration

Table 1 (continued)

Buprenorphine formulation (brand name, generic name, year of FDA approval)	Dose range	Formulations	Time to peak concentration (h)	Mean half-life (h)	Comments
Long-acting injectable (Buvidal [EU], Brixadi [USA], CAM-2038 q1w, approval in EU and tentative FDA approval 2018)	8–32 mg weekly	8 mg, 16 mg, 24 mg, 32 mg prefilled syringe	20	5 days	Subcutaneous injection in upper arm, abdomen, or buttocks; forms soft gel in subcutaneous space
Long-acting injectable (Buvidal [EU], Brixadi [USA], CAM-2038 q4w, approval in EU and tentative FDA approval 2018)	64–128 mg monthly	64 mg, 96 mg, 128 mg, 160 mg prefilled syringe	4–10	19–25 days	

EU European Union, FDA US Food and Drug Administration, *h* hours, *PRN* as needed, *q1w* every week, *q4w* every 4 weeks, *q6 h* every 6 h, *q12 h* every 12 h

subsequently marketed a sublingual film formulation of buprenorphine-naloxone that may have the advantage of faster absorption, and be easier to cut and divide into multiple daily doses if clinically required. Of note, controversy developed when Reckitt tried to block FDA approval of generic buprenorphine tablets, arguing that the tablets carried more risk of accidental ingestion by children and consequent risk of death, whereas a film formulation minimized this risk. Nonetheless, the FDA has approved the generic tablets, and generic films [72] are now also available.

11.2 Buprenorphine Implant

An implantable formulation of buprenorphine with a 6-month duration of action (brand name: Probuphine®) was approved by the FDA in 2016 for long-term maintenance treatment of opioid use disorder among patients who have been stable on 8 mg per day or less of sublingual buprenorphine. The implant consists of four plastic rods, each containing 80 mg of buprenorphine, inserted under the skin of the upper arm. Implantation involves a minor surgical procedure, which is straightforward. However, the rods also need to be removed after 6 months, which requires further surgical skill because the rods may migrate, attach to scar tissue, or fracture during the removal effort. The total dose of buprenorphine delivered by the implant (320 mg over 6 months, albeit parenterally) is modest, and the steady-state blood concentrations achieved fall in the 0.5- to 1.0-ng/mL range, consistent with trough concentrations achieved at steady state with 8 mg of sublingual buprenorphine.

Findings from clinical trials of the buprenorphine implant have been consistent with the modest dose delivered and relatively low blood concentrations of buprenorphine. A 6-month clinical trial among patients with active opioid use disorder newly admitted to treatment showed that the percentage of opioid-negative urine tests was relatively low (31%); this was superior to placebo, and non-inferior to a sublingual control condition targeting standard doses (12–16 mg per day) [73]. In contrast, a second clinical trial among patients stable on 8 mg per day or less of sublingual buprenorphine showed high levels of sustained abstinence when patients were started on the buprenorphine implant with an outcome that was non-inferior to the sublingual buprenorphine control [74]. This led to the FDA approval for maintenance treatment of patients stable on 8 mg or less of buprenorphine. This formulation may be attractive for patients who wish to be free of the burden of daily dosing, or as a transition off buprenorphine after a successful course of treatment. Because of the risks of implantation-site complications, the FDA developed a Probuphine risk evaluation and mitigation strategy program. This program requires providers to receive special training to prescribe, and to insert and remove the implants.

11.3 Extended-Release Injectable Buprenorphine

A subcutaneous injectable formulation with a 1-month duration of action (brand name: Sublocade[®]) has received FDA approval for the treatment of opioid use disorder following at least 7 days of transmucosal buprenorphine treatment. The injection comes in prefilled syringes, which require refrigeration until administered. Two dose levels are available: 300 mg (recommended as the starting dose) and 100 mg (which may be substituted after several months of successful treatment on the 300-mg dose). Sublocade uses the Atrigel[®] delivery system, which consists of poly (dl-lactide), lactide/glycolide copolymers, and a biocompatible solvent, *N*-methyl-2-pyrrolidone, forming a clear viscous liquid. It is injected under the skin of the abdomen and forms a solid depot upon exposure to the subcutaneous space, which then slowly dissolves over time. The average blood concentration observed in the month after the first 300-mg injection (2.19 ng/mL) was comparable to a concentration achieved between 12 mg/day (1.71 ng/mL) and 24 mg/day (2.91 ng/mL) of daily sublingual buprenorphine, although the steady-state values after 4-monthly injections were considerably higher (6.54 ng/mL after four 300-mg injections; 3.21 ng/mL after four 100-mg injections) [75].

A higher blood concentration could be an advantage in terms of achieving full occupancy and blockade of opioid receptors. A human laboratory study demonstrated that Sublocade 300 mg produced complete blockade of the effects of 8- and 16-mg doses of hydromorphone [76]. Blockade lasted for 8 weeks after the second injection, suggesting this formulation may be relatively forgiving to missed doses, or doses delivered later than the recommended 1-month intervals, as the blood concentration remains at therapeutic concentrations for some time beyond 4 weeks. This is a potential advantage among patients having difficulty with adherence to treatment. A phase III placebo-controlled clinical trial confirmed the superiority over placebo of regimens of a 300-mg injection monthly, or 300 mg for the first 2 months followed by 100 mg for the last 4 months, with just under 30% of patients achieving an 80% or greater proportion of opioid-negative urine tests over the 6-month trial. This trial did not include a sublingual buprenorphine comparison condition [75].

A second long-acting injectable formulation, CAM2038, is not yet marketed in the USA, but has had a successful phase III trial [77]. Approval was recently granted by the European Medicines Agency under the brand name Buvidal[®] and tentatively by the FDA under the brand name Brixadi[®]. CAM2038 comes in prefilled syringes for subcutaneous injection, with a range of weekly doses containing 8 mg, 16 mg, 24 mg, or 32 mg, and monthly duration doses containing 64 mg, 96 mg,

128 mg, or 160 mg, corresponding to sublingual doses ranging from the 8-mg/day to the 24- to 32-mg/day range. Thus, there is flexibility to titrate the dose. Unlike Sublocade, CAM2038 does not require refrigeration. CAM2038 formulates buprenorphine into a lipid-based liquid crystal technology, which transforms from an injected liquid to a solid gel upon entry into the subcutaneous space. The gel then slowly releases buprenorphine over either the 1-week or 1-month timeframe. A human laboratory study has demonstrated blockade of the effects of 6 mg and 18 mg of intramuscular hydromorphone over the week after the weekly 24-mg and 32-mg CAM2038 doses [78]. In a phase III clinical trial with sublingual buprenorphine as the control (flexibly dosed up to 24 mg/day) vs. a CAM2038 flexibly dosed weekly formulation for the first 12 weeks, then a monthly formulation for the subsequent 12 weeks, CAM2038 was non-inferior to sublingual buprenorphine on the primary outcome variable reflecting sustained abstinence, and superior on secondary outcomes, including opioid-negative urine tests over time [77].

In summary, the long-acting injectable formulations of buprenorphine seem likely to be useful additions to the therapeutic armamentarium for the treatment of opioid use disorder. They may be considered particularly for patients where adherence to daily sublingual buprenorphine is a problem.

12 Conclusions

Since its discovery in 1966 and the initial proposal for its use as a treatment for opioid use disorder in 1975, buprenorphine has been shown to be effective for the treatment of pain and medically supervised withdrawal or maintenance treatment of opioid use disorder. It is now widely used worldwide for the treatment of opioid use disorder, although most patients with opioid use disorder are still not receiving effective medication treatment, and more effort is needed to disseminate buprenorphine therapy across health systems. Numerous studies and meta-analyses have concluded that buprenorphine, at sufficient doses, is safe, improves treatment retention, and decreases illicit opioid use. In addition to its activity on the mu-opioid receptor, buprenorphine may also have therapeutic effects on mood through antagonism of the kappa opioid receptor. Although generally safe, there remains a risk of diversion, sedation, and overdose, especially when combined with other substances. Newer long-acting parenteral formulations of buprenorphine, mainly the long-acting injections, have the potential to improve adherence and thus expand on the effectiveness and dissemination of buprenorphine.

Compliance with Ethical Standards

Funding Matisyahu Shulman and Jonathan M. Wai were funded by the National Institute on Drug Abuse Grant T32 DA007294. Edward V. Nunes was funded by the National Institute on Drug Abuse Grant K24 DA022412 (PI: Nunes). The authors alone are responsible for the content and writing of this article. Manuscript preparation and the decision to submit the manuscript for publication were the sole responsibilities of the authors.

Conflict of interest Edward V. Nunes has served as an investigator on clinical trials for which Reckitt Benckiser Inc. supplied Suboxone, and for which Alkermes, Inc. supplied Vivitrol for study medication, and has served as a consultant without compensation on advisory boards to Alkermes, Inc. Matisyahu Shulman and Jonathan M. Wai have no conflicts of interest that are directly relevant to the content of this article.

References

- Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrera A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018;5(12):987–1012.
- Center for Behavioral Health Statistics and Quality (CBHSQ). 2015 National Survey on Drug Use and Health: detailed tables. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2016.
- Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001;58(5):503–8.
- World Health Organization. Department of Mental Health, Substance Abuse, World Health Organization, International Narcotics Control Board, United Nations Office on Drugs, Crime. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009.
- Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatry*. 2015;23(2):63–75.
- Walker R, Logan TK, Chipley QT, Miller J. Characteristics and experiences of buprenorphine-naloxone use among polysubstance users. *Am J Drug Alcohol Abuse*. 2018;44(6):595–603.
- Williams A, Nunes E, Olfson M. To battle the opioid overdose epidemic, deploy the ‘cascade of care’ model. *Health affairs blog*. 2017. <https://www.healthaffairs.org/doi/10.1377/hblog20170313.059163/full/>. Accessed 20 Nov 2018.
- Preston A, Bennett G. The history of methadone and methadone prescribing. In: Strang J, Tober G, editors. *Methadone matters: evolving community methadone treatment of opiate addiction*. Taylor and Francis Group: London; 2003. p. 13–20.
- Garrido MJ, Trocóniz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. *J Pharm Toxicol Methods*. 1999;42(2):61–6.
- Kreek MJ, Vocci FJ. History and current status of opioid maintenance treatments: blending conference session. *J Subst Abuse Treat*. 2002;23(2):93–105.
- Dole VP, Nyswander MA. Medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA*. 1965;193(8):646–50.
- Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. *Arch Intern Med*. 1966;118(4):304–9.
- Ball J, Corty E, Bond H, Myers C, Tommasello A. The reduction of intravenous heroin use, non-opiate abuse and crime during methadone maintenance treatment: further findings. *NIDA Res Monogr*. 1988;81:224–30.
- Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*. 1998;93(4):515–32.
- Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts’ risk of fatal heroin overdose. *Subst Use Misuse*. 1996;31(2):177–96.
- Kuhlman JJ Jr, Lalani S, Magluilo J Jr, Levine B, Darwin WD, Johnson RE, et al. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol*. 1996;20(6):369–78.
- Lewis JW. Buprenorphine. *Drug Alcohol Depend*. 1985;14(3–4):363–72.
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.
- Deck D, Carlson MJ. Access to publicly funded methadone maintenance treatment in two western states. *J Behav Health Serv Res*. 2004;31(2):164–77.
- Calcaterra SL, Bach P, Chadi A, Chadi N, Kimmel SD, Morford KL, et al. Methadone matters: what the United States can learn from the global effort to treat opioid addiction. *J Gen Intern Med*. 2019. <https://doi.org/10.1007/s11606-018-4801-3> (**Epub ahead of print**).
- Fatseas M, Auriacombe M. Why buprenorphine is so successful in treating opiate addiction in France. *Curr Psychiatry Rep*. 2007;9(5):358–64.
- Jaffe JH, O’Keeffe C. From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug Alcohol Depend*. 2003;70(2 Suppl.):S3–11.
- Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Am J Public Health*. 2015;105(8):e55–63.
- Kissin W, McLeod C, Sonnefeld J, Stanton AJ. Experiences of a national sample of qualified addiction specialists who have and have not prescribed buprenorphine for opioid dependence. *J Addict Dis*. 2006;25(4):91–103.
- Hutchinson E, Catlin M, Andrilla CH, Baldwin LM, Rosenblatt RA. Barriers to primary care physicians prescribing buprenorphine. *Ann Fam Med*. 2014;12(2):128–33.
- Schaub M, Chtenguelov V, Subata E, Weiler G, Uchtenhagen A. Feasibility of buprenorphine and methadone maintenance programmes among users of home made opioids in Ukraine. *Int J Drug Policy*. 2010;21(3):229–33.
- Michie G, Hoosain S, Macharia M, Weich L. Report on the first government-funded opioid substitution programme for heroin users in the Western Cape Province, South Africa. *S Afr Med J*. 2017;107(6):539–42.
- Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann N Y Acad Sci*. 2012;1248(1):124–39.
- Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry*. 1978;35(4):501–16.
- Peckham AM, De La Cruz A, Dufresne RL. Kappa opioid receptor antagonism: are opioids the answer for treatment resistant depression? *Ment Health Clin*. 2018;8(4):175–83.
- Ehrich E, Turncliff R, Du Y, Leigh-Pemberton R, Fernandez E, Jones R, et al. Evaluation of opioid modulation in major depressive disorder. *Neuropsychopharmacology*. 2015;40(6):1448–55.
- Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use: the international experience. *Clin Infect Dis*. 2006;43(Suppl. 4):S197–215.

33. Rao R, Agrawal A, Kishore K, Ambekar A. Delivery models of opioid agonist maintenance treatment in South Asia: a good beginning. *Bull World Health Organ.* 2013;91:150–3.
34. ElKashef A, Alzayani S, Shawky M, Al Abri M, Littlewood R, Qassem T, et al. Recommendations to improve opioid use disorder outcomes in countries of the Middle East. *J Subst Use.* 2018;24(1):4–7.
35. Himmich H, Madani N. The state of harm reduction in the Middle East and North Africa: a focus on Iran and Morocco. *Int J Drug Policy.* 2016;1(31):184–9.
36. Himmich H, Kazatchkine MD, Stimson GV. Drug policy and human rights in the Middle East and North Africa: harm reduction, legal environment and public health. *Int J Drug Policy.* 2016;1(31):4–5.
37. SOSFS 2004:8. Socialstyrelsens föreskrifter och allmänna råd om läkemedelsassisterad behandling vid opioidberoende (The National Board of Health and Welfare's regulations and general advice about drug-assisted treatment with opioids). In: Gemensamma författningssamlingen avseende hälso- och sjukvård, socialtjänst, läkemedel, folkhälsa m.m. (Common constitutional collection regarding healthcare, social services, medicines, public health, etc.). Sweden: Ödman, Par, National Board of Health and Welfare; 2016. <https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20053/2016-2-3.pdf>. Accessed 12 Mar 2019.
38. Rao R. The journey of opioid substitution therapy in India: achievements and challenges. *Indian J Psychiatry.* 2017;59:39–45.
39. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep.* 2010;12:448–53.
40. Auriacombe M, Franques P, Martin C, Lafitte C, Afflelou S, Bertorelle V, et al. Follow-up of a cohort of opioid dependent subjects in methadone and buprenorphine maintenance treatment: impact on quality of life. *Eur Psychiatry.* 1997;12:157s.
41. Fatseas M, Dubernet J, Daoulouede JP, Auriacombe M. Buprenorphine in the treatment of opioid addiction: the French experience. In: el-Guebaly N, Carrà G, Galanter M, editors. *Textbook of addiction treatment: international perspectives.* Springer: Milan; 2015. p. 501–10.
42. Dupouy J, Palmaro A, Fatséas M, Auriacombe M, Micallef J, Oustric S, et al. Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. *Ann Family Med.* 2017;15(4):355–8.
43. PCSS. Discover the rewards of treating patients with opioid use disorders. 2019. <https://pcssnow.org>. Accessed 18 Apr 2019.
44. Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid medically supervised withdrawal and naltrexone induction strategies: recommendations for clinical practice. *Am J Drug Alcohol Abuse.* 2012;38(3):187–99.
45. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, et al. Buprenorphine tapering schedule and illicit opioid use. *Addiction.* 2009;104(2):256–65.
46. Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, et al. Multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid, medically supervised withdrawal: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction.* 2005;100(8):1090–100.
47. Weiss RD, Potter JS, Griffin ML, Provost SE, Fitzmaurice GM, McDermott KA, et al. Long-term outcomes from the national drug abuse treatment clinical trials network prescription opioid addiction treatment study. *Drug Alcohol Depend.* 2015;150:112–9.
48. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry.* 2011;68(12):1238–46.
49. Ravndal E, Amundsen EJ. Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study. *Drug Alcohol Depend.* 2010;108(1–2):65–9.
50. Seaman SR, Brettle RP, Gore SM. Mortality from overdose among injecting drug users recently released from prison: database linkage study. *BMJ.* 1998;316(7129):426–8.
51. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, et al. Release from prison: a high risk of death for former inmates. *N Engl J Med.* 2007;356(2):157–65.
52. Bird SM, Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99. *Addiction.* 2003;98(2):185–90.
53. Kosten TR, Kleber HD. Buprenorphine medically supervised withdrawal from opioid dependence: a pilot study. *Life Sci.* 1988;42(6):635–41.
54. Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid medically supervised withdrawal with naltrexone versus buprenorphine. *Am J Psychiatry.* 2017;174(5):459–67.
55. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction.* 2014;109(1):79–87.
56. Hser YI, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction.* 2016;111(4):695–705.
57. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet.* 2011;377(9776):1506–13.
58. Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA Jr, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med.* 2016;374(13):1232–42.
59. Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet.* 2018;391(10118):309–18.
60. Das S, Sah D, Nandi S, Das P. Opioid withdrawal presenting as delirium and role of buprenorphine: a case series. *Indian J Psychol Med.* 2017;39(5):665.
61. Lee JD, Vocci F, Fiellin DA. Unobserved “home” induction onto buprenorphine. *J Addict Med.* 2014;8(5):299–308.
62. Kenney SR, Anderson BJ, Conti MT, Bailey GL, Stein MD. Expected and actual fentanyl exposure among persons seeking opioid withdrawal management. *J Subst Abuse Treat.* 2018;86:65–9.
63. Carroll KM, Weiss RD. The role of behavioral interventions in buprenorphine maintenance treatment: a review. *Am J Psychiatry.* 2016;174(8):738–47.
64. Galanter M, Dermatis H, Glickman L, Maslansky R, Sellers MB, Neumann E, et al. Network therapy: decreased secondary opioid use during buprenorphine maintenance. *J Subst Abuse Treat.* 2004;26(4):313–8.
65. Auriacombe M, Fatséas M, Dubernet J, Daoulouede JP, Tignol J. French field experience with buprenorphine. *Am J Addict.* 2004;1(13 Suppl. 1):S17–28.
66. Post S, Spiller HA, Casavant MJ, Chounthirath T, Smith GA. Buprenorphine exposures among children and adolescents reported to US poison control centers. *Pediatrics.* 2018;142(1):e20173652.

67. Saxon AJ, Ling W, Hillhouse M, Thomas C, Hasson A, Ang A, et al. Buprenorphine/naloxone and methadone effects on laboratory indices of liver health: a randomized trial. *Drug Alcohol Depend.* 2013;128(1–2):71–6.
68. Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Medically supervised withdrawal from opiate drugs during pregnancy. *Am J Obstet Gynecol.* 2016;215(3):374.e1–6.
69. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010;363(24):2320–31.
70. Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle EL, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction.* 2016;111(12):2115–28.
71. Disher T, Gullickson C, Singh B, Cameron C, Boulos L, Beaubien L, et al. Pharmacological treatments for neonatal abstinence syndrome: a systematic review and network meta-analysis. *JAMA Pediatr.* 2019. <https://doi.org/10.1001/jamapediatrics.2018.5044>.
72. BusinessWire. Amneal Pharmaceuticals received FDA approval for generic Suboxone®. 2019. <https://www.businesswire.com/news/home/20130225005607/en/Amneal-Pharmaceuticals-Receive-FDA-Approval-Generic-Suboxone%C2%AE>. Accessed 18 Apr 2019.
73. Rosenthal RN, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction.* 2013;108(12):2141–9.
74. Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. *JAMA.* 2016;316(3):282–90.
75. Indivior United Kingdom. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s0001bl.pdf. Accessed 13 Mar 2019.
76. Nasser AF, Greenwald MK, Vince B, Fudala PJ, Twumasi-Ankrah P, Liu Y, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol.* 2016;36(1):18–26.
77. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern Med.* 2018;178(6):764–73.
78. Walsh SL, Comer SD, Lofwall MR, Vince B, Levy-Cooperman N, Kelsh D, et al. Effect of buprenorphine weekly depot (CAM2038) and hydromorphone blockade in individuals with opioid use disorder: a randomized clinical trial. *JAMA Psychiatry.* 2017;74(9):894–902.